UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETYAND POLLUTION PREVENTION

MEMORANDUM

Date: November 14, 2019

SUBJECT: **Fipronil:** Tier II Incident and Epidemiology Report

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Summary and Conclusions

This memo is the Fipronil Tier II Incident and Epidemiology Report. Prior to this memo, fipronil incidents were last reviewed in March 2011 (S. Recore, D387320, 3/01/2011). In 2011, the Health Effects Division (HED) prepared a preliminary Tier I human incident review of fipronil human incident reports by consulting the Office of Pesticide Programs (OPP) Incident Data System (IDS) for reports of poisoning incidents. In 2011, a moderately large number of incidents were reported involving fipronil. At the time, given the frequency and relative severity, HED determined it would further evaluate fipronil acute poisoning event reporting and surveillance databases as well as a review of published literature on the acute and chronic health effects associated with fipronil exposure by performing a Tier II review.[1]

For this Fipronil Tier II Incident and Epidemiology Report, HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report. These health effects primarily involve neurological, dermal, ocular, and respiratory symptoms. HED did not identify

[1] For this review, no medical case reports were investigated.

any aberrant effects outside of those anticipated. These effects were generally mild/minor to moderate and resolved rapidly. In both IDS and SENSOR-Pesticides, exposure to pet products is the most often reported exposure scenario.[2] For NPIC and CA PISP, post-application exposure following application to an individual's home was the most often reported exposure scenario.[3] The IDS trend over time from 2009 to 2018 for fipronil incidents appears to be decreasing.

Epidemiological studies investigating the association between fipronil and health outcomes available in the open literature were reviewed. Overall, there was insufficient evidence to suggest a clear associative or causal relationship exists between fipronil exposure and the health outcomes investigated in the studies reported here. The Agency will continue to monitor the epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted.

1 BACKGROUND

Fipronil is a broad-spectrum insecticide belonging to the phenylpyrazole class of insecticides. It is registered for use on agricultural commodities corn (seed for export only) and potato, as well as for ornamentals, turfgrass, forestry and in/around agricultural/manufacturing/industrial areas. Residential home-use products include those used to treat outdoor ant pests and turfgrass, as well as indoor applications as a flea and tick preventative for pets, a subsurface termiticide, and as crack and crevice insecticide.

HED is currently re-evaluating the toxicity, exposure, and risk profile of fipronil under the Food Quality Protection Act (FQPA)-mandated Registration Review program. The registration review program is designed to ensure EPA evaluates new information regarding pesticides on a 15-year cycle, and to update the risk assessment and initiate new regulatory requirements, when appropriate, to ensure the protection of human health and the environment. Pesticides included in the registration review program are pesticides for which EPA completed a Re-registration Eligibility Decision under the FQPA.

One component of the Agency's Registration Review Program is consideration of acute and chronic health effects observed in the human population as a possible consequence of fipronil exposure. Given the frequency observed in the initial screening evaluation of acute poisoning incidents related to fipronil use, HED determined that a more extensive Tier II report of the acute and chronic human health effects linked to fipronil use should be performed.

A Tier II incident and epidemiology report, as compared to a Tier I incident and epidemiology report, provides additional details and greater depth in scope of review of information relating to human exposure. Utilization of these data will aid HED in better defining and characterizing the potential risk of fipronil pesticide products to the U.S. population, and particular sub-groups such as workers and children.

This Fipronil Tier II Incident and Epidemiology Report reviews human observation data from a variety of sources including:

- Human incident (poisoning) data from the following sources:
    - OPP's Incident Data System (IDS) database;
    - National Institute of Occupational Safety and Health (NIOSH) SENSOR-Pesticides;

[2] For IDS, 78% of the incidents were attributed to exposure to pet products. For SENSOR-Pesticides, 65% of the incidents were attributed to exposure to pet products.
[3] For NPIC, 73% of the incidents were attributed to post-application exposure following application to an individual's home. For CA PISP, 57% of the incidents were attributed to post-application exposure following application to an individual's home.

- National Pesticide Information Center (NPIC) (Agency Sponsored); and,
- California's Pesticide Incident Surveillance Program (PISP).

- Epidemiological studies from the open literature.

Incident data are collected systematically, but differently, across the different databases used by the Agency with respect to such issues as coverage, certainty/confidence, fields/parameters reported, and usability. The four pesticide incident data sources (IDS, NIOSH SENSOR-Pesticides, NPIC, and California PISP) were used in this fipronil report since they provide useful content and historical perspective. Various other comparable sources of data are available (*e.g.*, the Bureau of Labor Statistics, emergency room outpatient surveillance, National Poison Data System (NPDS), etc.) but are not included in this review. By looking across the four data sources which were used, the Agency is confident that we are considering adequate and appropriate information to discern trends and patterns in fipronil-associated acute pesticide poisonings, or "incidents."

It is important to recognize, however, that reports of adverse health effects allegedly due to a specific pesticide exposure (*i.e.*, an "incident") are largely self-reported and therefore, generally speaking, neither exposure to a pesticide nor reported symptoms (or the connection between the two) are validated. Therefore, only rarely can causation be determined or definitively identified based on incident data. However, incident information can provide important feedback to the Agency. Human incident data, in concert with other human observational studies (biomonitoring and epidemiological studies) and the human health risk assessment, can assist the Agency in determining potential risks of pesticides/pesticide product exposure, and can help characterize that risk. This review assesses acute pesticide poisoning incidents and published epidemiology studies to inform the preliminary risk assessment for fipronil.

2 REVIEW OF HUMAN INCIDENT DATA

2.1 OPP Incident Data System (IDS) (2014-2019)

The OPP IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 60(a)(2) reports from registrants and reports from other federal and state health and environmental agencies and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contains reports from across the U.S. and most incidents contained in the system have all relevant product information recorded. Case reports or "narratives" are provided for each incident with varying levels of detail; however, there is no effort at validating or assessing how likely it is that the reported exposure is causally related to the reported outcome. Because IDS has such extensive coverage, it is useful for providing temporal trend and geographic pattern information. The system is also useful for determining whether risk mitigation has helped reduce potential pesticide exposure through a decreased number of reported incidents.

For this evaluation, the OPP IDS was utilized for pesticide incident data on the active ingredients fipronil (PC Code: 129121). IDS records incidents in one of two modules: Main IDS and Aggregate IDS. Main IDS contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics. This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one active ingredient (as opposed to pesticide products with multiple active ingredients) are considered to provide more certain information about the potential effects of exposure from the pesticide. The higher severity outcomes include:

- H-A (death): If the person died;

- H-B (major): If the person alleged or exhibited symptoms which may have been life-threatening, or resulted in adverse reproductive effects or in residual disability; and
- H-C (moderate): If the person alleged or exhibited symptoms more pronounced, more prolonged or of a more systemic nature than minor symptoms, usually some form of treatment of the person would have been indicated, symptoms were not life threatening and the person has returned to his/her pre-exposure state of health with no additional residual disability.

Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries. The less severe human incidents include:

- H-D (minor): If the person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involve skin, eye or respiratory irritation; and
- H-E (unknown or no effects): If symptoms are unknown, unspecified or are alleged to be of a delayed or chronic nature that may appear in the future.

For the Main IDS, from January 1, 2014 to August 20, 2019, there are 210 cases reported that involve the active ingredient fipronil.[4,5] Forty-four of these incidents involved the single active ingredient fipronil only and the other 166 incidents involved multiple active ingredients.

Of the 210 incidents involving fipronil, there was one death reported. This incident occurred in Massachusetts in 2016. A 47-year-old male had been exposed to the product annually when it was used to treat the outside of his home. He passed away. No further details available. There were four incidents classified as major severity, 176 incidents classified as moderate severity, and 29 incident classified as minor severity.[6] The death and major severity incidents are described in **Appendix A, Table 1**.

Of the fipronil incidents reported to Main and Aggregate IDS from January 1, 2014 to August 20, 2019, most of the incidents are attributed to pet spot-on products (74%). Twenty two percent are attributed to pet sprays and 4% were attributed to products used around the home but not on pets.

Eighty-two incidents occurred in the two years from 2017 to 2019 and were further reviewed for exposure scenario and reported symptoms. These incidents are described in **Appendix A, Table 2**. Of the 82 fipronil incidents further reviewed for this analysis, most (62%) involve individuals reporting exposure to fipronil during application of the product to a pet. Two of these incidents involved spray products and 49 incidents involved spot-on products. The second most reported exposure scenarios (31%) are secondary exposure to a pet that has been treated with fipronil product by someone else. These incidents involved spot-on products. The complete list of exposure scenarios is in **Table 1**.

[4] There were also forty-four incidents that occurred in Australia (1), Belgium (4), Brazil (16), Denmark (3), England (4), France (2), Germany (9), Italy (2), Spain (1), and Switzerland (2). Foreign incidents are not reviewed in detail because of the potential differences in the exposure patterns, use practices, and product formulation.

[5] It should be noted there was one incident reported as a lawsuit to IDS that was not considered in this report.

[6] Minor severity incidents and "no effects" incidents are typically reported to the Aggregate IDS but do occasionally get reported to the Main IDS. For fipronil, there are 1,262 more incidents reported to Aggregate IDS from 2014 to August 20, 2019.

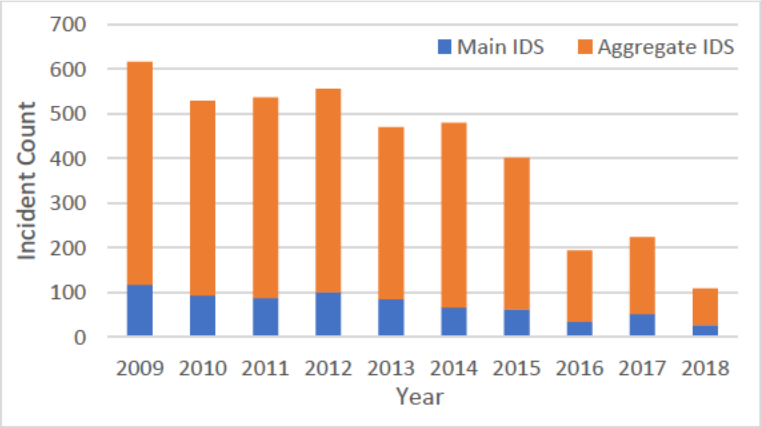
Table 1. Exposure Scenario Frequency of Fipronil Incidents Reported to Main IDS (2017-2019)	
Exposure Scenario	Number of Reported Incidents
Exposure during application to pet	51
Secondary exposure to treated pet	16
Postapplication exposure that occurred following application to the individual's home (6 by a professional applicator, 1 by home applicator)	7
Homeowner applicator	2
Leaking from package	1
Intentional harm (alleged poisoning attempt)	1
Dermal contact with bait station	1
Accidental occupation exposure	1
Accidental misuse	1
Accidentally sprayed	1

Based on the IDS reports, symptoms most often reported were dermal (n = 45), neurological (n = 24), ocular (n = 14), respiratory (n = 12), gastrointestinal (n = 11), and cardiovascular (n = 2). Note that a patient could exhibit multiple symptoms. Dermal symptoms reported include irritation, redness, bumps, hives, welts, rash, itchiness, dermatitis, sloughing skin, blisters, and swelling. Neurological symptoms reported include muscles aches, tingling sensation, dizziness, loss of balance, vertigo, nerve pain, shaking, convulsions, and headache. Ocular symptoms reported were irritation, itchiness, burning, watering, and blurry vision. Respiratory symptoms reported included shortness of breath, asthma, difficulty breathing, sneezing, throat irritation, and coughing. Gastrointestinal symptoms reported were diarrhea, abdominal pain, nausea, and vomiting. Cardiovascular symptoms reported include fast heart rate, elevated blood pressure, and heart palpitations.

In Aggregate IDS, queried from January 1, 2014 to August 20, 2019, there are 1,262 incidents involving fipronil. Five of these incidents were classified as having no or unknown effects and 1,257 incidents were classified as minor severity. Minor severity means that a person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involved skin, eye or respiratory irritation. Because these incidents fall within the categories reported as counts (which includes minor, unknown or no effects), there is no unique report that provides details about the incident and single chemical incidents are not distinguished from multiple chemical incidents; however, in general a high frequency of incidents may indicate that there is a high potential for exposure or elevated acute toxicity and vice versa.

In both Main and IDS databases combined, pet products (spot-ons and sprays) were implicated in 78% of the incidents reported. Spot-on products were implicated in 74% of the total incidents reported. The fipronil incident trend, from 2009 to 2018, appears to be decreasing over time (Figure 1).

Figure 1. Fipronil Incidents Reported to IDS from 2009 to 2018



2.2 SENSOR-Pesticides (2011-2015)

The Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (CDC/NIOSH) manages a pesticide surveillance program and database entitled the Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides.[7] All cases must report at least two adverse health effects. Evidence for each case is evaluated for its causal relationship between exposure and illness based on the NIOSH case classification index.[8] Using standardized protocol and case definitions, SENSOR-Pesticides state coordinators, operating out of the state's department of health, receive state pesticide incident reports from local sources, then follow up with case sources to get the incident scenario to obtain medical records and verify exposure scenario information.[9] This database includes pesticide illness case reports from multiple states from 1998-2015.[10]

A query of SENSOR-Pesticides from 2011-2015 identified a total of 71 cases involving fipronil. Thirty-six cases involved a single active ingredient and 34 cases involved multiple active ingredients. Sixty-two cases were low in severity and eight cases were moderate in severity. The majority of cases were non-occupational (n = 56). Most cases were exposed while applying pet products or were exposed to pet product residue. The complete list of exposure scenarios is in **Table 2**.

Table 2. Exposure Scenario Frequency of Fipronil Incidents Reported to SENSOR-Pesticides (2011-2015)

Exposure Scenario	Number of Reported Incidents
Exposed to a flea product for dogs or cats	46
Exposed to ant bait products	6

[7] SENSOR-Pesticides webpage: http://www.cdc.gov/niosh/topics/pesticides/overview.html.
[8] https://www.cdc.gov/niosh/topics/pesticides/pdfs/casedef.pdf
[9] https://www.cdc.gov/niosh/topics/pesticides/pdfs/pest-sevindexv6.pdf
[10] Currently participating states are: California, Florida, Illinois, Louisiana, Michigan, Nebraska, New Mexico, North Carolina, Oregon, Texas and Washington. The participating states for a given year vary depending on state and federal funding for pesticide surveillance.

Exposed to roach bait products	5
Exposed to termite products	10
Exposed to agricultural products	4

Cases reported a variety of symptoms across body systems: 31 cases reported nervous system symptoms (primarily headache and dizziness), 30 cases reported an ocular symptom, 22 cases reported a gastrointestinal symptom, 24 cases reported a dermal symptom, and 22 cases reported a respiratory symptom. Cases could report symptoms in multiple body systems. Recall 89% of fipronil-related cases in SENSOR-Pesticides were low in severity and resolved rapidly and without medical care. Specific symptoms most frequently reported among the 70 fipronil cases were: 1) eye pain/inflammation, 2) nausea, 3) headache, 4) dizziness, 5) vomiting, 6) swelling of skin and 8) upper respiratory pain/irritation.

2.3 National Pesticide Information Center (NPIC) (2013-2019)

The National Pesticide Information Center or NPIC is a cooperative effort between Oregon State University and EPA which is funded by EPA to serve as a source of objective, science-based pesticide information and respond to inquiries from the public and to incidents. NPIC functions nationally during weekday business hours through a toll-free telephone number in addition to the internet (www.npic.orst.edu) and email. Similar to Poison Control Centers, NPIC's primary purpose is not to collect incident data, but rather to provide information to inquirers on a wide range of pesticide topics and direct callers for pesticide incident investigation and emergency treatment. Nevertheless, NPIC does collect information about incidents (approximately 4000 incidents per year) from inquirers and records that information in a database. NPIC is a source of national incident information but generally receives fewer reports than IDS. Regardless, if a high frequency is observed in IDS, NPIC provides an additional source of information to see whether there is evidence of consistency across national data sets or possibly duplication and additional information about the same incident(s).

From January 1, 2014 to May 14, 2019, 72 human incidents involving fipronil were reported to NPIC. NPIC estimates a certainty index as to whether an incident (including reported symptoms)[11] was consistent or inconsistent (formerly definitely, probably, possibly, or unlikely) with the reported exposure to a pesticide, or whether the incident was unrelated to pesticides or if the incident was unclassifiable. Of the 72 reported incidents, 26 were reported as symptomatic, classified as consistent with fipronil exposure, and were further reviewed. Six of the 26 reviewed incidents were classified as moderate severity and 20 were classified a minor severity. Of the 26 incidents reviewed, most individuals reported being exposed during post-application following application to the individual's home. The complete list of exposure scenarios is in **Table 3**.

Table 3. Exposure Scenario Frequency of Fipronil Incidents Reported to NPIC (2013-2019)

Exposure Scenario	Number of Reported Incidents
Post-application exposure that occurred following application to the individual's home (16 by a professional applicator, 3 by home applicator)	19
Exposure during application to pet	2

[11] Starting in mid-2015, NPIC switch from using definitely, probably, possibly, or unlikely to using consistent or inconsistent for the certainty index.

Table 3. Exposure Scenario Frequency of Fipronil Incidents Reported to NPIC (2013-2019)	
Exposure Scenario	Number of Reported Incidents
Secondary exposure to treated pet	3
Accidental contact with the product during application	1
Professional applicator accidentally inhaled the product during exposure	1

Forty-six incidents were not further reviewed. Eighteen incidents were not reviewed because they were asymptomatic and designated as unclassifiable. Twenty-six incidents were classified as being unlikely or inconsistent with fipronil exposure. Finally, two incidents were not classified by NPIC because the symptoms were unknown.

The 26 symptomatic incidents were further reviewed for reported symptoms. Based on the NPIC reports, symptoms most often reported were neurological (n = 14), respiratory (n = 8), dermal (n = 7), ocular (n = 3), gastrointestinal (n = 3), and cardiovascular (n = 3). Note that a case could exhibit multiple symptoms. Neurological symptoms reported headache, tingling, numbness, loss of balance, speech difficulty, dizziness, disorientation, seizure, and altered taste. Respiratory symptoms reported included wheezing, difficulty breathing, throat irritation, postnasal drip, and coughing. Dermal symptoms reported include burning sensation, sores, blisters, skin irritation, swelling, rash and itchiness. Ocular symptoms reported were eye irritation and burning. Gastrointestinal symptoms reported were nausea, vomiting, and diarrhea. Cardiovascular symptoms reported include chest pain, chest tightness, and erratic heart rate.

2.4 California Pesticide Illness Surveillance Program (PISP) (2012-2016)

The Pesticide Illness Surveillance Program (PISP) maintains a database of pesticide-related illnesses and injuries. Case reports are received from physicians and via workers' compensation records. The local County Agricultural Commissioner investigates circumstances of exposure. Medical records and investigative findings are then evaluated by DPR technical experts and entered into an illness registry.

PISP contains both residential and occupational pesticide incidents. PISP has limited coverage (only California) and is therefore not useful for identifying national trends over time. However, the incident information is entered by professionals with expertise in pesticides who extensively follow-up on each reported case, establishing a high degree of confidence in the information provided for each reported incident.

In PISP from 2012 to 2016 there were 35 case reports involving fipronil. All of cases were non-agricultural cases. Twenty-eight of these cases were classified as having a possible relationship to fipronil and seven of these cases were classified as having probable relationship with fipronil.[12] Most (57%) individuals reported being exposed during the post-application period following application to the individual's home. The complete list of exposure scenarios is in **Table 4**.

[12] A **possible** relationship indicates that health effects correspond generally to the reported exposure, but evidence is not available to support a relationship.
A **probable** relationship indicates that limited or circumstantial evidence supports a relationship to pesticide exposure.

Table 4. Exposure Scenario Frequency of Fipronil Incidents Reported to CA PISP (2012-2016)	
Exposure Scenario	Number of Reported Incidents
Postapplication exposure that occurred following application to the individual's home	20
Professional applicator exposure	4
Child ingestion	4
Exposure during application to pet	3
Homeowner accidental contact with the product during application	1
Misuse (applied product directly to self)	1
Mixer/loader application	1
Off-site movement through window from professional application outside home	1

The symptoms most often reported were neurological (n = 22), respiratory (n = 17), gastrointestinal (n = 13), ocular (n = 10), dermal (n = 6), and cardiovascular (n = 1). Note that a patient could exhibit multiple symptoms. Neurological symptoms reported include dizziness, headache, weakness, numbness, and tingling. Respiratory symptoms reported included shortness of breath, throat irritation, wheezing, coughing, difficulty breathing, hoarseness, and dry mouth. Gastrointestinal symptoms reported were diarrhea, abdominal pain, nausea, and vomiting. Ocular symptoms reported were irritation, itchiness, redness, burning, stinging, pain, and broken blood vessel. Dermal symptoms reported include hives, rash, redness, and burning sensation. Cardiovascular symptoms reported include elevated blood pressure.

2.5 Literature Review

HED reviewed *Acute illnesses associated with exposure to fipronil—surveillance data from 11 states in the United States, 2001–2007* (Lee et al., 2010). In this article, Lee et al. (2010) analyzed incidents from SENSOR-Pesticides and California PISP and found that a total of 103 cases were identified in 11 states. The authors found that the majority (76%) had exposure in a private residence, 37% involved the use of pet-care products, and 26% had work-related exposures. Most of the cases (89%) had mild temporary health effects. The most commonly reported symptoms were neurological symptoms (50%) such as headache, dizziness, and paresthesia, followed by ocular (44%), gastrointestinal (28%), respiratory (27%), and dermal (21%) symptoms/signs. The authors state that exposures usually occurred from inadvertent spray/splash/spill of products or inadequate ventilation of the treated area before re-entry. They concluded that exposure to fipronil can pose a risk for mild temporary health effects in various body systems.

2.6 Acute Incident Summary

HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report. These health effects primarily include neurological, dermal, ocular, and respiratory. HED did not identify any aberrant effects outside of those anticipated. These effects are generally mild/minor to moderate and resolve rapidly.

In both IDS (78%) and SENSOR-Pesticides (65%), exposure to pet products were responsible for most of the exposures reported. For NPIC (73%) and CA PISP (57%), post-application exposure following application to an individual's home was the most often reported exposure scenario. In all four databases, most of the reported incidents occurred in private residences. In addition, the health effects and exposure scenarios discussed in reviewed article (Lee et al., 2010) correspond to those reported to IDS, SENSOR-Pesticides, NPIC, and CA PISP for the years covered in this memorandum.

Fipronil incident trends over time from 2009 to 2018 were reviewed in IDS. Based on these data, which are primarily exposure to pet spot-on cases, incidents appear to be decreasing over time.

3 REVIEW OF PUBLISHED EPIDEMIOLOGY

3.1 Introduction

As part of registration review, EPA's OPP is responsible for determining if there is new data or information that warrants a new human health risk assessment. To support this effort, OPP conducted a systematic literature review of peer reviewed epidemiology studies that examined the association between fipronil and adverse health effects. The specific aims of the epidemiology literature review were to:

1. Conduct a literature search and assemble a database of epidemiological studies examining the human health effects associated with fipronil exposure; and,
2. Review, summarize, and assess the quality of the assembled literature.

This report describes the systematic literature review approach and results of OPP's evaluation of epidemiology study findings. This evaluation focused on characterizing results and identifying strengths and limitations with respect to health outcomes evaluated in the literature. Specific sections of this report will include a description of the literature search and methodology and evaluation approach, a synthesis of findings by health outcomes evaluated in the literature, and finally a summary of conclusions.

3.2 Review Framework

The National Academy of Sciences National Research Council (NRC) and the National Academy of Medicine (formerly the Institute of Medicine) define systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. In a 2014 report, NRC identified systematic literature review strategies as "appropriate for EPA" and "specifically applicable to epidemiology and toxicity evaluations."[13]

EPA OPP published a framework for incorporating epidemiological data into risk assessments for pesticides which described a systematic review process relying on standard methods for collecting, evaluating, and integrating the scientific data supporting Agency decisions.[14] The epidemiology framework characterized "fit for purpose" systematic reviews for incorporating human epidemiology data into OPP risk assessments for pesticides, meaning that the complexity and scope of each systematic review is tailored to a specific analysis and follows the key characteristics outlined in the Cochrane Handbook:[15]

[13] NRC. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press.
[14] US EPA. December 28, 2016. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf
[15] Higgins, J. P., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions* (Vol. 4). John Wiley & Sons.

- Clearly stated set of objectives with pre-defined eligibility criteria for studies;
- Explicit, reproducible methodology;
- Systematic search to identify all relevant studies;
- Assessment of the validity of the findings from the identified studies; and,
- Systematic presentation and synthesis of the characteristics and findings of the included studies.

Following the procedures described in the OPP epidemiology framework, OPP conducted a formalized literature review to collect, evaluate, and integrate evidence from relevant epidemiological literature on the association between fipronil exposure and human health outcomes to evaluate whether exposure to this chemical is associated with an increased (or decreased) risk of adverse health outcomes.

3.3 Literature Search Methodology

3.3.1 Systematic Literature Search

The literature search methodology followed the guidance provided in the National Toxicology Program/Office of Health Assessment and Translation (NTP/OHAT*) Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration,* January 9, 2015. For the search, the following population, exposure, comparator, and outcome of interest (PECO) criteria below guided the inclusion/exclusion criteria and selection of term:

- **Population of interest:** Population studied must be humans with no restrictions, including no restrictions on age, life stage, sex, country of residence/origin, race/ethnicity, lifestyle, or occupation
- **Exposure:** Exposure studied must be to fipronil in any application via any route of exposure.
- **Comparator:** Exposed or case populations must be compared to a population with low/no exposure or to non-cases to arrive at a risk/effect size estimate of a health outcome associated with fipronil exposure.
- **Outcome:** All reported human health effects, with no restrictions on human system affected (effects could be based on survey or other self-report, medical records, biomarkers, publicly available health data, or measurements from human sample populations).

Based on these PECO criteria, inclusion/exclusion terms were identified, and a literature search was conducted in PubMed, PubMed Central, Science Direct, and Web of Science. The literature search included all published articles through September-2019. Results were limited to those with human subjects and an English language abstract. The search code used to identify articles is listed in **Table 5**.

Table 5. Fipronil Literature databases, search strategies, search dates, and articles returned.[16]

Database	Search Strategy	Search Date	Articles Returned
Web of Science	("fipronil" OR "termidor" OR "fluocyanobenpyrazole" OR "pestanal") AND (human AND (epidemiologic stud* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud* OR ecological stud*))	9/17/2019	39

[16] The number of articles reported reflects a net return and does not consider duplicates (the same article returned in multiple databases and/or multiple times in one database).

Database	Search Strategy	Search Date	Articles Returned
Science Direct	("fipronil") AND (human AND (epidemiologic stud* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud*))	9/17/2019	542
PubMed	(fipronil OR fipronil sulfone OR termidor OR fluocyanobenpyrazole OR pestanal) AND (epidemiolog* stud* OR epidemiolog* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud* OR adverse health outcome* OR expos*)) AND human	9/19/2019	88
PubMed Central	((fipronil OR fipronil sulfone OR termidor OR fluocyanobenpyrazole OR pestanal) AND (epidemiolog* stud* OR epidemiolog* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud* OR adverse health outcome* OR expos*)) AND "humans"[MeSH Terms]	9/25/2019	191

* indicates truncation (*i.e.,* that alternate endings were searched)

Based on the PECO criteria and search terms described above, the literature search aimed to identify original, peer-reviewed articles on epidemiologic studies. Exclusion criteria were also identified prior to collecting potentially relevant publications. Articles were excluded for the following reasons: not full text (*e.g.,* abstracts); not peer-reviewed; not in English; non-human study subjects; in-vitro studies; fate and transport studies; outcome other than human health effects (*e.g.,* environmental measures); experimental model system studies; no fipronil-specific investigation (*e.g.,* general herbicide); no risk/effect estimate reported (*e.g.,* case studies/series); no original data (*e.g.,* review publications).[17] In addition, the review focused on epidemiology studies and excluded articles on acute poisonings and overexposure.

A key element of the inclusion/exclusion criteria hinged on the definition of "human health effect" outcomes. For the purposes of the epidemiology literature review, OPP HED considered human health effects via the toxicological paradigm presented by the NRC as pathologies or health impairments subsequent to altered structure/function.[18] Thus, studies with outcomes of altered structure (*e.g.,* DNA alteration, sister chromatid exchange, cell proliferation) or biomarker or other exposure outcomes (*e.g.,* in breast milk, urine, cord blood, or plasma) that did not also include an associated health pathology (*e.g.,* cancer, asthma, birthweight) failed to meet the inclusion criteria for "human health effects" for the purposes of this epidemiology literature review.

3.3.2 Supplemental Literature Search

To supplement the open literature search described above, OPP reviewed publications resulting from the Agricultural Health Study (AHS) for articles that satisfied the inclusion/exclusion criteria. The AHS is a federally funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA.

[17] While the search focused on original peer-reviewed articles, the OPP does seek out and consider other sources of information that are not peer-reviewed (e.g. letters to the editor, corrections, commentary) on a case-by-case basis when this information provides clarification or other material findings or information of relevance to our evaluation of the literature.
[18] Henderson, R., Hobbie, J., Landrigan, P., Mattisoti, D., Perera, F., Pfttaer, E., ... & Wogan, G. (1987). Biological markers in environmental health research. Environmental Health Perspectives, 7, 3-9.

The AHS maintains on its website an electronic list of publications resulting from AHS studies using the AHS cohort.[19] These articles were imported into Endnote (Clarivate Analytics, vX9.2), and Endnote was used to run a full text search ("Any Field + PDF with Notes") for "Fipronil", to ensure all AHS publications relevant to the epidemiology literature review were identified. AHS articles that satisfied the inclusion/exclusion criteria as described above were selected for inclusion in the epidemiology literature review.

The final phase of data collection was a reference review of articles captured in the open literature search, the AHS publication search, and previously published OPP documents. References were examined to identify relevant publications that were not captured in either the open literature search or the AHS publication search. Resulting articles from this reference review that satisfied inclusion/exclusion criteria were selected for inclusion in the epidemiology literature review.

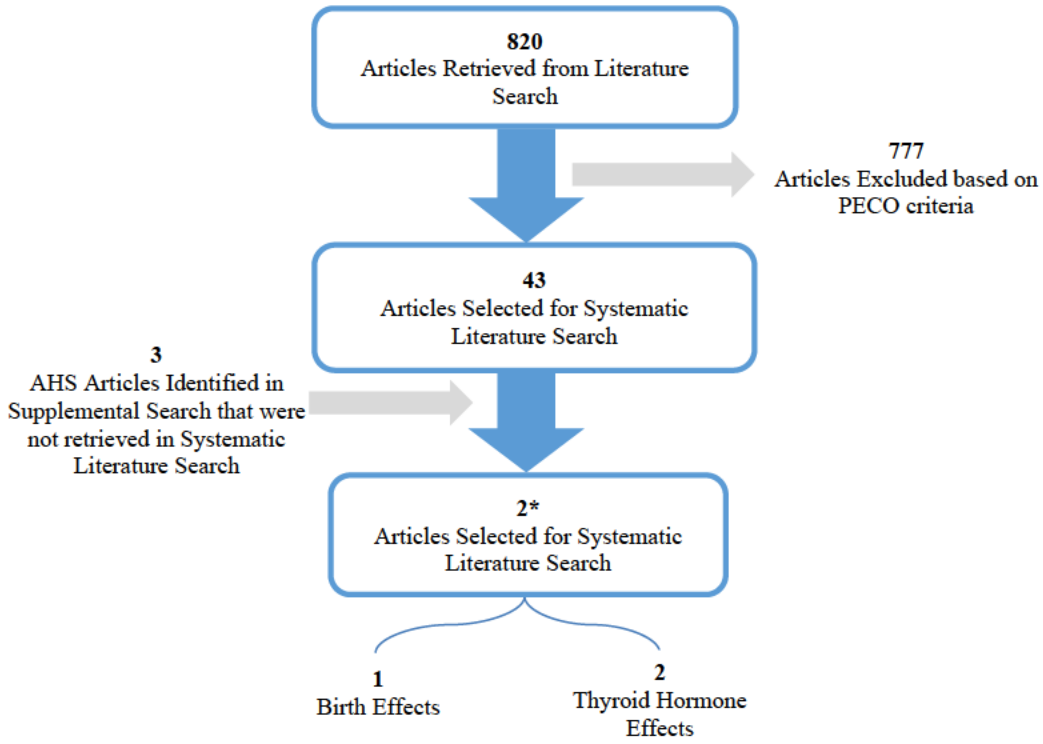
3.3.3 Literature Search Results

The search of the open literature returned 820 unique articles across PubMed, PubMed Central, Science Direct, and Web of Science and these articles were assembled into an EndNote Library (version X8) (40 duplicates were removed). The title and abstract of each article were screened for potential relevance using the PECO criteria and exclusion criteria described in the **Systematic Literature Search section**. EPA identified 43 articles based on this approach and no additional articles were identified that were cited by the articles screened during reference review. Of these 43 articles reviewed, 41 did not include fipronil-specific analysis. This yielded a total of two articles that reported effect estimates for fipronil exposure.

The supplemental search of the AHS EndNote Database identified an additional three articles that included the term "fipronil" in their text or tables. The three articles (Alavanja et al., 2007; Deziel et al., 2016; and Deziel et al., 2018) were reviewed, but did not include fipronil-specific analysis. Thus, review of the AHS articles did not yield any additional articles that reported effect estimates for fipronil exposure. A summary of the literature search and supplemental AHS search is provided in **Figure 2**.

[19] Agricultural Health Study Publications: https://aghealth nih.gov/news/publications.html

Figure 2: Summary of Literature Search Results.



** Number of articles on health outcomes do not sum because some articles reported on multiple outcomes in a single article.*

3.4 Literature Review and Evaluation Approach

3.4.1 Study Review and Quality Assessment

A total of two peer-reviewed epidemiologic articles were identified for OPP's literature review and evaluation. Each article was reviewed and relevant information on study design, results, conclusions, strengths, and weaknesses of each study was summarized per the epidemiology framework (US EPA, 2016), and details recounted include the exposure measurement, outcome ascertainment, number of participants (n), number exposed/number of cases, number in reference (un-exposed/control) group, effect measure (*e.g.,* odds ratio (OR), relative risk (RR), hazard ratio (HR)) and associated estimates of uncertainty and/or statistical significance (*e.g.,* confidence interval (CI), p-value), confounders considered, and methods of analysis. OPP considered these elements in assessing the quality of each publication and its applicability to an overall assessment of the health effects associated with fipronil exposure.

The assessment of study quality followed the OPP Framework. As shown in **Table 6**, the study quality assessment considered aspects such as design, conduct, analysis, and interpretation of study results, including whether study publications incorporated a clearly articulated hypothesis; adequate assessment of exposure; critical health windows; valid and reliable outcome ascertainment; a sample representative of the target population; analysis of potential confounders; characterization of potential systematic biases; evaluation and reporting of statistical power; and use of appropriate statistical modeling techniques.

Table 6: Epidemiology Study Quality Considerations. Adapted from Table 2 in US EPA (2016).

Parameter	High	Moderate	Low
Exposure assessment	Exposure assessment includes information on fipronil or metabolite in the body, quantitative air sample data, or high-quality questionnaire on chemical-specific exposure assessment during relevant exposure window	Questionnaire based individual level information on fipronil	Low quality questionnaire-based exposure assessment, or ecologic exposure assessment, with or without validation
Outcome Assessment	Standardized tool, validated in study population; or, medical record review with trained staff	Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated	Subject report, without additional validation
Confounder control	Good control for important confounders relevant to fipronil study question, and standard confounders	Moderately good control of confounders, standard variables, not all variables for fipronil study question	Multi-variable analysis not performed, no adjustments
Statistical Analysis	Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)	Acceptable methods, questionable study power (esp. sub-analyses), analytic choices that lose information, not reported clearly	Minimal attention to statistical analyses, comparisons not performed or described clearly
Risk of (other) bias (selection, differential misclassification, other)	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding

Note: Overall study quality ranking based on comprehensive assessment across the parameters.

Study design influenced the assessment of study quality. Cohort studies, which enable researchers to assess the temporality of exposure in relation to health outcome and to consider multiple health outcomes, were generally considered higher quality than other study designs. Case-control studies, which are susceptible to recall bias, were generally considered to be of lower quality than nested case-control studies, which may be less susceptible to selection and recall bias. Cross-sectional studies cannot distinguish temporality for exposure in relation to health outcomes; therefore, cross-sectional studies were generally considered lower quality than cohort or case-control studies and were regarded as hypothesis-generating in the absence of additional studies supporting an observed association. The lowest quality study design considered was ecologic, due to an inability to extrapolate observed associations from the group level to the individual level (ecological fallacy) inherent in the ecologic study design. Ecologic studies were generally regarded as hypothesis-generating studies (US EPA, 2016).

Studies that characterized the exposure-response relationship (*e.g.,* with a dose-response curve or trend statistic) were, in general, considered higher quality than studies that did not characterize exposure-response. Studies that specified temporality (*i.e.,* those that determined exposure preceded a health outcome) and studies that specified or explored uncertainties in the analysis were, in general, considered higher quality than studies that failed to specify temporality and studies that lacked an examination of uncertainty. Consistent results between study groups (*e.g.,* a significant and positive association seen for both farmers and commercial applicator study groups within a single study) bolstered the assessment of study quality.

Risk estimates (estimates of effect) reported in epidemiological studies were generally considered as follows:

- No evidence of a positive association between exposure and outcome (*e.g.,* OR ≤ 1.00);
- No evidence of a significant positive association (*e.g.,* OR > 1.00 but not significant);
- Evidence of a slight positive association (*e.g.,* 1.00 < OR < 1.30 and significant);
- Evidence of a positive association (*e.g.,* 1.30 ≤ OR < 2.0 and significant);
- Evidence of a moderately strong (*e.g.,* 2.0 ≤ OR < 3.0 and significant) or strong (*e.g.,* OR ≥ 3.0 and significant) positive association.[20]

However, we recognize that results that fail to attain statistical significance may still indicate clinical, biological, and/or public health importance and may warrant further exploration (US EPA, 2016). We particularly noted large observed associations (*e.g.,* OR ≥ ~2.5) even in the absence of significance, perhaps indicating a smaller than optimal sample size.

3.4.2 Categories of Evidence

Table 7 describes the categories of evidence which are guided by several documents that have been developed by EPA and others. These include as a main reference, a document developed by the Institute of Medicine (now the Academies of Science, Engineering, and Medicine)[21] which detailed various "Categories of Association" which describes guidance for drawing conclusions regarding the overall strength of the evidence that exists regarding any putative linkage between an exposure and a health effect (IOM, 1998). Also considered in developing OPP's categories of evidence were the NTP's OHAT document on systematic review and evidence integration (Woodruff and Sutton, 2014), OPP's epidemiologic framework document (US EPA, 2016), and EPA's Preamble to the Integrated Science Assessments which serve as a scientific foundation for the review of EPA's National Ambient Air Quality Standards (US EPA, 2016).[22]

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[20] For articles that reported ORs, RRs, and HRs, the confidence interval (CI) acted as a proxy for significance testing, with CIs that do not contain the null value (OR / RR / HR = 1.00) considered significant. P-value significance considered a critical value of α = 0.05 unless otherwise specified by the authors and noted in the summaries here.

[21] IOM (1998). Veterans and Agent Orange Update 1998. National Academy Press. Washington, DC. https://www nap.edu/read/6415/chapter/1. Some of this material is derived from and/or consistent with U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004 and its Chapter 1 "Introduction and Approach to Causal Inference", available at: https://www ncbi nlm nih.gov/books/NBK44695/. Much of this material is also presented in a more recent National Academies publication from 2018: National Academies of Sciences, Engineering, and Medicine 2018. *Gulf War and Health: Volume 11: Generational Health Effects of Serving in the Gulf War*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25162.

[22] U.S. EPA. Preamble To The Integrated Science Assessments (ISA). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-15/067, 2015.

In this memorandum, each category is assigned based on a case-by-case approach that considers the weight of the epidemiological evidence and expert judgement and not a binding or inflexible formulaic approach in deciding the number and/or quality of studies that would be necessary to assign a specific evidence category. When assigning a level of evidence category to an exposure and the body of evidence pertaining to that health effect, the level of quality of the studies available in the peer-reviewed literature for that health effect, the strength of the associations (effect sizes) and consistency of the association in magnitude and direction across available studies was considered, as described in OPP's epidemiologic framework document.

Table 7: Categories of Evidence.

Evidence Category	Description
Sufficient Epidemiological Evidence of a Clear Associative or Causal Relationship	*Sufficient epidemiological evidence to suggest a clear associative or causal relationship between the exposure and the outcome.* There is high confidence in the available evidence to suggest that a clear associative or causal relationship exists between the exposure and the health outcome of interest. Studies are minimally influenced by chance, bias, and confounding. Further, additional epidemiological data, evidence, or investigations are unlikely to substantively affect the overall magnitude or direction of the observed association or result in a meaningful change with respect to any conclusions regarding this association. This level of evidence might be met, for example, if several high- or moderate- quality studies on different study populations, by different authors, in different settings, and/or using different epidemiological study designs that are likely to be minimally influenced by bias and confounding show a clear associative or causal relationship that is consistent among studies with respect to magnitude and direction of effect sizes. Such evidence is strengthened when one or more high- or moderate-quality studies also demonstrate dose-response trends with the range of these doses (exposures) considered sufficient to cover the range of expected human exposure levels (including the high end) and the evidence base consists of a least one high-quality prospective cohort study.
Limited but Insufficient Epidemiological Evidence of an Association	*Limited but insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.* There is some confidence that the available evidence accurately reflects a clear association between the exposure and the outcome, but the evidence is limited because the studies are of insufficient quantity, quality, (internal) validity, or consistency or because chance, bias, and confounding could not be ruled out with confidence. While the present body of evidence suggests that a relationship between exposure and disease outcome may possibly exist, additional high- or moderate-quality epidemiological data, evidence, or investigations could affect the overall magnitude or direction of the observed associations and might result in a meaningful change to this level of evidence category. This level of evidence category might be met, for example, if the body of evidence is: (1) based at least on one high-quality study suggesting a statistically significant relationship and the results of other high or moderate quality studies are mixed, contradictory, imprecise, ambiguous, or inconsistent; (2) based on several moderate-quality studies which show a relationship between exposure and outcome that is less pronounced than in (1); or (3) based on many studies (both moderate and possibly low-quality studies) showing a generally consistent direction and for which additional and more thorough analysis would be needed to make the determination of a relationship.

Evidence Category	Description
Insufficient Epidemiological Evidence of an Association	*Insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.* There is minimal confidence in the available evidence that the findings accurately reflect an association between the exposure and the outcome because the studies are of insufficient quantity, quality, (internal) validity, consistency, or statistical power to permit a conclusion to be reached, and/or chance, bias, or confounding may play an important role and cannot be ruled out. Further, additional high- or moderate-quality epidemiological data, evidence, or investigations could substantively affect the overall magnitude or direction of any observed associations. This level of evidence category might be met, for example, if the body of evidence is: (1) too small to permit conclusions, such as when there are no available studies to validate or corroborate the findings of a single moderate- or low-quality study; (2) based entirely on one or more studies judged to be of low-quality; or (3) based on multiple moderate- or low-quality studies, but the heterogeneity of exposures, outcomes, and methods leads to mixed, conflicting, imprecise, ambiguous, or contradictory conclusions.
No Epidemiological Evidence of an Association	*No epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.* There is no epidemiological evidence to suggest the presence of an association between an exposure and outcome. This level of evidence category might be met, for example, if the body of evidence consists of high- or moderate-quality studies that show no evidence of a statistically significant association and generally appear to have small effect sizes, and/or for which chance, bias, or confounding may play an important role.
Sufficient Evidence of No Causal Relationship	*Sufficient epidemiological evidence to suggest there is no causal relationship between the exposure and the outcome.* There is high confidence in the available evidence to suggest there is no causal relationship between the exposure and the outcome. The studies are minimally influenced by chance, bias, and confounding, and it is unlikely that additional epidemiological data, evidence, or investigations would meaningfully affect the current overall magnitude, direction, or conclusions about the association. This level of evidence category might be met, for example, if at least one high-quality study with adequate power (*e.g.,* ≥80%) to detect a meaningful effect size determined to be of substantive importance fails to show an effect and no other high or moderate quality studies provide affirmative evidence against this null result. In addition, data would also exist that suggests no significant dose-response trends are present with the range of these doses (exposures) considered sufficient to cover the range of expected human exposure levels (including the high end) and the evidence base consists of a least one high-quality prospective cohort study.

3.5 Literature Review and Evaluation

This section presents a review and evaluation of the epidemiologic literature on the potential association between fipronil exposure and adverse health outcomes. The review and evaluation is organized by health outcome, and includes *Birth Effects* and *Thyroid effects*. For each of the health outcome sections, individual study articles are summarized and then an overall evaluation of findings is characterized. **Appendix B** provides an additional tabular summary of both studies with respect to their design, methods, results, and study quality.

3.5.1 Birth Effects

One study (Kim et al., 2019) investigated the association between prenatal fipronil exposure and birth effects in neonates.

> Kim et al. (2019) examined the potential association between *in utero* exposure to fipronil and several birth outcomes in a cross-sectional study of a birth-cohort of mother-infant and biological father triads in South Korea.[23] The study population included healthy pregnant women-newborn pairs (n = 59) and the matching biological father (n = 51) who were recruited prior to delivery. Women who received prenatal care from Inje University Ilsan Paik Hospital in South Korea between March 2013 and July 2015 and delivered their newborn infants at 31 - 41 weeks of gestation were eligible to participate. Maternal and paternal blood was collected when the mother visited the hospital for delivery and newborn infant umbilical cord blood was collected during delivery. Fipronil and fipronil sulfone (a primary metabolite of fipronil) levels were tested in serum using liquid chromatography electrospray ionization mass spectrometry. Blood samples were stored at -80°C and all laboratory technicians were blinded to outcome status. Method and matrix blanks were used for each analysis, and reagent blanks and Quality Control (QC) samples were used for each instrumental run. The limits of detection (LOD) for fipronil and fipronil sulfone were 0.027 ng/mL and 0.087 ng/mL, respectively. Serum fipronil (parent compound) levels from study participants were not detectable above the LOD (except for one paternal serum sample).[24] Fipronil sulfone, on the other hand, was detected in serum samples from all study participants and thus only serum fipronil sulfone (the metabolite) levels were considered in the analysis for the study. Fipronil sulfone levels were highest in the paternal samples (geometric mean +/- geometric standard deviation = 1.163 ± 0.797 ng/mL, range, 0.130 – 3.570 ng/mL) and were significantly higher than fipronil sulfone levels in either maternal serum samples (0.744 ± 0.426 ng/mL, range, 0.0790 – 2.910 ng/mL) or infant cord blood samples (0.525 ± 0.240 ng/mL, range, 0.159 –1.750 ng/mL). Demographic and pregnancy health data were collected via one-on-one interview and questionnaires completed by both parents at the time of blood sampling, and included questions on age, Body Mass Index (BMI), weight gain during gestation, waist circumference, age of menarche, duration of menstrual cycle, history of dysmenorrhea and related surgeries, gravity, parity, cigarette smoking, alcohol consumption, exposure to second-hand smoke, physical activity, owning a cat or dog, and various socioeconomic characteristics. Medical records provided current or previous parental health status and newborn birth outcomes (*e.g.*, infant sex, birth weight, birth length, head circumference, ponderal index, and birth morbidity).[25]
>
> A number of birth outcomes were investigated including: gestational age, birth weight, birth length, head circumference, ponderal index, Apgar score at one minute and Apgar score at five minutes.[26] Two multiple linear regression models (Model I and Model II) were used to evaluate the potential association between the main fipronil metabolite (fipronil sulfone) and adverse birth outcomes. Model I was adjusted for maternal age, maternal pre-pregnant BMI, parity (primipara or multipara), smoking status (maternal indirect smoking status, yes/no), parental education levels, household income, infant sex, gestational age, birth weight, birth length, head

[23] Kim et al. also investigated thyroid hormone levels in the infants, and this is covered under the Thyroid Effects section of this review.
[24] This paternal serum sample fipronil concentration was measured at 0.12 ng/mL.
[25] Birth morbidity was defined as infants with a diagnosis of one or more of the following: intraventricular hemorrhage; respiratory distress syndrome; bronchopulmonary dysplasia; and necrotizing enterocolitis.
[26] Results for infantile thyroid hormones including: triiodothyronine (T3), thyroxine (T4); free triiodothyronine (Free T3); free thyroxine (Free T4); and thyroid-stimulating hormone (TSH) are reported in the **Thyroid Hormone Effects** section.

circumference, and Ponderal index.[27] Model II included all of the above-mentioned covariates in addition to birth morbidity, Apgar score at one minute, and Apgar score at five minutes.

For gestational size outcomes,[28] no evidence of a statistically significant association was reported between fipronil sulfone levels in infantile cord blood serum and gestational age, birth weight, head circumference, birth length, or ponderal index for either model (Model I: -14.368 < all β < 0.092; all 95% CI encompassed the null value 0; all p-values > 0.05; Model II: -0.004 < all β < 5.965; all 95% CIs encompassed the null value 0; all p-values > 0.05).[29]

With respect to Apgar scores, mean Apgar scores in the newborn infants at one minute and at five minutes were 7.85 ± 1.19 (5-10) and 9.07 ± 0.64 (7-10), respectively, and were within normal range for a healthy infant (7-10).[30] While no evidence of a significant association was reported for *Apgar score at one minute* in newborn infants for either model[31] (*Model I* − β = −0.217; 95%CI: -1.132, 0.697, p = 0.65; *Model II* − β = 0.375; 95%CI: -0.430, 1.180, p = 0.37), evidence of a statistically significant association was reported for prenatal fipronil exposure and decreased *Apgar score at five minutes in newborn infants* in both models (*Model I* − β = -0.538; 95%CI: -1.061, - 0.015, p = 0.04; *Model II* − β = -0.477; 95%CI: -0.902, -0.051, p = 0.03).

The overall quality of the study was ranked low based on the study quality criteria in the OPP Framework. Study strengths included the hospital-based determination of the birth outcome measures as well as the laboratory quality control associated with the fipronil exposure measures. Limitations included the cross-sectional study design and the use of a single blood sample to quantify pesticide exposure. Since the pesticide exposure marker and birth outcomes were measured contemporaneously in this cross-sectional study, it is unclear if the associations observed provide direct evidence of a temporal relationship between fipronil exposure and the birth outcomes assessed in the study. And, the use of a single blood sample taken a birth may not accurately reflect relevant past, longitudinal, or longer-term exposure patterns. With respect to the statistical analyses that were performed, we note three additional concerns:

- No background or rationale was provided with respect to how the independent (predictor) variables were selected for consideration or for inclusion in the model; the dataset consisted of only 59 mother-infant pairs (or 51 mother-father-infant triads) and 12 (or more) factors were incorporated as covariates, some of which were likely highly correlated themselves (*e.g.*, parental education levels and household income). Given the limited sample size, the number of covariates included in the model is likely to be excessive and may lead to statistical bias.[32] Further, no indication was provided by the

[27] Equal to the birth weight in grams divided by the third power of body length (cm), then multiplied by 100.
[28] Infant gestational size outcomes included (Mean ± standard deviation (SD) (range)): gestational age: 37.44 ± 2.59 weeks (30.6–41.0); birth weight: 2,983.66 ± 547.09 g (1,710–3,940); head circumference 33.11 ± 1.92 cm (28.5–36.0); birth length 48.57 ± 2.76 cm (41.5–53.5); and ponderal index 2.51 ± 0.19 g/cm^3 (2.16–2.97)
[29] Regression coefficients (95% CI) were as follows for Model I and Model II, respectively: *gestational age (weeks)* – -0.343 (-1.940, 1.254) and 0.109 (-1.604, 1.822); *birth weight (g)* – -14.368 (-65.946, 37.211) and 5.965 (-44.652, 56.583); *head circumference (cm)* – -0.089 (-1.176, 0.997) and -0.183 (-1.312, 0.946); *birth length (cm)* – 0.092 (-0.204, 0.388) and -0.018 (-0.310, 0.275); *ponderal index (g/cm^3)* – 0.014 (-0.029, 0.056) and -0.004 (-0.045, 0.038).
[30] Watterberg, K. L., Aucott, S. W., Benitz, W. E., Cummings, J. J., Eichenwald, E. C., Goldsmith, J., ... & Ecker, J. L. (2015). The Apgar Score. *Pediatrics*, *136*(4), 819-822. See also Apgar, Virginia . A proposal for a New Method of Evaluation of the Newborn Infant, reprinted in Anesthesia and Analgesia, May 2015 120(5): 1056-1059 and available for download at https://journals.lww.com/anesthesia-analgesia/pages/articleviewer.aspx?year=2015&issue=05000&article=00022&type=Fulltext#pdf-link
[31] The study authors reported p-values as either <0.05 or <0.05. These were recalculated and listed here based on the upper and lower 95% confidence intervals that were reported in the article.
[32] For example, see OPP's Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides" (December 28 2016) at https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf where we

authors that any regression diagnostics or other formal model testing were performed to indicate that multiple regression model assumptions were met or that the most appropriate model was selected.

- Additionally, the study performed multiple comparisons without correction for multiple comparisons (*e.g*, false discovery rate corrections) which increases the likelihood of spurious (and thus non-repeatable) findings. For this reason, the study is considered to be exploratory and hypothesis-generating in nature.
- Finally, two of the measured outcomes (Apgar score at 1 minute and Apgar score at 5 minutes are not independent and likely to be highly correlated. Further, the measure is used as means to rapidly summarize a newborn's health against infant mortality and has not been tested or validated for the purposes of this study. The measure is coarse, summarizing each of five separate test evaluations (Appearance, Pulse, Grimace, Activity, and Respiration) on a 0 - 2 points scale and then summing these scores up for a total Apgar score of up to ten points. It is typically used in a hospital to determine if an infant needs immediate medical care and its utility or relevance with respect to predicting either subtle congenital conditions or longer-term health issues is not clear.33

EPA Conclusion

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between fipronil exposure and adverse effects with respect to birth outcome parameters. The one available study that examined birth effects was cross-sectional in design and assessed exposure by measuring fipronil sulfone metabolite in blood at only one time. The study also evaluated a large number of associations between the serum metabolite fipronil sulfone and a number of different birth outcome parameters without correction for multiple comparisons. Further, there were a several statistical concerns about the study that further limited the quality of the study. The findings are summarized in **Table 8** below.

Table 8: Summary of Epidemiological Evidence on Fipronil Exposure and Birth Effects

Study	Study Population	Study Design[1]	Study Quality[2]	Gestational Age (weeks)	Birth Weight (g)	Head circumference (cm)	Birth length (cm)	Ponderal index (g/cm^3)	Apgar Score	
									at 1 minute	at 5 minutes
Kim et al. (2019)	Hospital-based birth-cohort of 51 parent-infant triads in South Korea	CS	L	⊘	⊘	⊘	⊘	⊘	⊘	↓●

⊘ No evidence of an association between exposure and outcome ($p > 0.05$).

● Evidence of a significant association ($p < 0.05$).

↑ - Positive association. ↓ - Negative association.

[1] Study Design –*CS* = Cross-Sectional

[2] Study Quality –*L* = Low

state: "When performing statistical modeling when the outcome is rare or the sample size is relatively small, it is important to be cautious about including too many covariates in the model. Any resulting effect size estimate may be too high or too low and is unlikely to reflect the true estimate of effect… Thus: while controlling for confounders and other covariates is important, the assessor must take care not to over-control or end up with too few degrees of freedom to produce a reliable test. In these cases, it may be more important to seek parsimonious models that adjust for only a smaller number of the most influential confounders and other covariates so that the effective sample size remains adequate."

[33] Bovbjerg, M. L., Dissanayake, M. V., Cheyney, M., Brown, J., & Snowden, J. M. (2019). Utility of the 5-minute Apgar Score as a Research Endpoint. *American Journal of Epidemiology*, 188(9), 1695-1704.

3.5.2 Thyroid Hormone Effects

Two studies (Herin et al., 2003; Kim et al., 2019) examined the effects of fipronil exposure on thyroid hormone effects in neonates in South Korea and in adult factory workers in France.

Thyroid Hormone Effects in Neonates

One study (Kim et al., 2019) investigated the association between prenatal exposure to fipronil and thyroid hormone effects in neonates.

Kim et al. (2019) examined the potential association between *in utero* exposure to fipronil and several birth outcomes (reviewed above) and thyroid hormone levels in a cross-sectional study of a birth-cohort of parent-infant triads in South Korea. Specifically, infant thyroid hormone measurements included triiodothyronine (T3); thyroxine (T4); free triiodothyronine (Free T3); free thyroxine (Free T4); and thyroid-stimulating hormone (TSH). The study population included healthy pregnant women-newborn pairs and the matching biological father who were recruited prior to delivery. The study is described in further detail in the **Birth Effects** section of this memorandum and birth outcomes are reported there as well. Infantile thyroid hormone outcomes are reported below. Evidence of a significant inverse association was reported for infantile fipronil sulfone levels for both decreased cord blood *T3* (Model I − β = -0.104; 95% CI: -0.177, -0.029, p = 0.006; Model II − β = -0.105; 95% CI : -0.190, -0.020, p = 0.02) and decreased cord blood *Free T3 levels* (Model I − β = -0.021; 95%CI: -0.037, -0.004, p = 0.01; Model II − β = -0.021; 95%CI: -0.040, -0.002, p = 0.03), but no evidence of a significant association was reported between fipronil sulfone and infantile Free T4, T4, and TSH.[34, 35]

The overall quality of the study was ranked low based on the study quality criteria in the OPP Framework. The hospital-based laboratory quality control associated with the fipronil exposure measures was a study strength. Study limitations included most importantly the cross-sectional study design and use of a single blood sample to quantify pesticide exposure and serum hormone levels. Since the pesticide exposure marker and the hormone levels were measured contemporaneously in this cross-sectional study, it is unclear if the associations observed provide direct evidence of a temporal relationship between pesticide exposure and the hormone levels assessed, and this approach may not accurately reflect relevant past, longitudinal, or longer-term exposure patterns. As all but one of the fipronil measures were < LOD, measures of fipronil sulfone, a major metabolite of fipronil, that has a longer half-life and is more persistent in the environment were used in the analysis. The association between parental fipronil sulfone levels and infant outcomes was illustrated but not assessed. With respect to the statistical analyses that were performed, we note two additional concerns:

- No background or rationale was provided with respect to how the independent (predictor) variables were selected for consideration or for inclusion in the model; the dataset consisted of only 59 mother-infant pairs (or 51 mother-father-infant triads) and 12 (or more) factors were incorporated as covariates, some of which were likely highly correlated themselves (*e.g.*, parental education levels and household income). Given the limited sample size, the number of covariates included in the model is likely to be

[34] The study authors reported p-values as either <0.05 or >0.05. These were recalculated and listed here based on the upper and lower 95% confidence intervals that were reported in the article.

[35] Infant thyroid hormone measurements included triiodothyronine (T3); thyroxine (T4); free triiodothyronine (Free T3); free thyroxine (Free T4); and thyroid-stimulating hormone (TSH). Infant serum thyroid hormones levels (Mean ± SD (range)) were: T3: 0.59 ± 0.08 ng/mL (0.41–0.80); T4: 8.06 ± 1.21 ug/dL (5.55–10.69); Free T3: 0.13 ± 0.02 ng/dL (0.08–0.19); Free T4: 1.25 ± 0.14 ng/dL (0.99–1.58); and, TSH: 10.98 ± 6.70 uIU/mL (2.97–40.55).

excessive and may lead to statistical bias.[36] Further, no indication was provided by the authors that any regression diagnostics or other formal model testing were performed to indicate that multiple regression model assumptions were met or that the most appropriate model was selected.

- Additionally, the study performed multiple comparisons without corrections for false discovery rate which increases the likelihood of spurious (and thus non-repeatable) findings. Thus, the study is considered to be exploratory and hypothesis generating in nature.

Thyroid Hormone Effects in Adults

One study (Herin et al., 2011) investigated the association between fipronil exposure and thyroid function in adults.

Herin et al. (2011) investigated the association between fipronil exposure and abnormal thyroid function in adults in a cross-sectional analysis of factory workers that manufactured fipronil-containing veterinary drugs in France. The authors used data collected from a descriptive epidemiology survey of the fipronil exposed factory workers in 2008 for their analysis. The study population included 159 factory workers (80 males, 79 females) with exposure to fipronil while working at a factory in France (~10% of all factory workers). Exposure was assessed through measurements of fipronil and the major metabolite, fipronil sulfone, in serum samples collected from all exposed workers present the day of the survey. Demographic and occupational characteristics were abstracted from occupational medical records. Serum concentrations of thyroid hormones TSH, total T4, and Free T4 were measured using an automated immunoassay and direct chemiluminescence detection. Liquid chromatography-mass spectrometry was used to detect concentrations of fipronil and fipronil sulfone with LOD and limits of quantification of 0.1 μg/L and 0.2 μg/L, respectively. Laboratory standards were used, validation procedures were performed daily for five days, and intra-assay and inter-assay precision, accuracy and recovery were examined. Spearman's rank correlation coefficients were used to evaluate the potential correlations between fipronil and fipronil sulfone concentrations and serum TSH, Total T4 (TT4), and Free T4 concentrations. The 159 exposed workers were stationed at any one of ten work stations in the factory at which there was exposure to fipronil; the mean duration of occupational exposure to fipronil was four years (range: 1 - 11 years, SD 3.6 years). Fipronil was detected in the serum of 33 workers and fipronil sulfone was detected in serum of 155 workers. Mean fipronil and fipronil sulfone concentrations were 0.47 μg/L (SD: 0.28) and 7.79 μg/L (SD: 7.65, range: 0.37 - 42.45 μg/L), respectively. Eighteen of the 159 workers exposed to fipronil had one or more abnormal thyroid hormone level measurements.[37] Specifically, seven had elevated TSH, one had low TSH, three had low Free T4, and 11 had high TT4.[38] Based on these results, the authors stated that six of the workers (or 3.8% of the study population) had subclinical hypothyroidism, (defined as elevated TSH with normal Free T4). Two of the workers had

[36] For example, see OPP's Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides" (December 28 2016) at https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf where we state: "When performing statistical modeling when the outcome is rare or the sample size is relatively small, it is important to be cautious about including too many covariates in the model. Any resulting effect size estimate may be too high or too low and is unlikely to reflect the true estimate of effect… Thus: while controlling for confounders and other covariates is important, the assessor must take care not to over-control or end up with too few degrees of freedom to produce a reliable test. In these cases, it may be more important to seek parsimonious models that adjust for only a smaller number of the most influential confounders and other covariates so that the effective sample size remains adequate."

[37] Reference intervals for TSH, TT4, and Free T4 were 0.4-4.4 µIU/mL, 4.5- 10.9 µg/dL, and 10.7–21.1 pmol/L, respectively.

[38] Two of the 11 workers with elevated TT4 concentrations were being treated with levothyroxine and had low or normal TSH.

elevated serum TT4 and decreased serum Free T4. A significant negative correlation was reported between serum fipronil sulfone and TSH concentration[39] (TSH Spearman's rank correlation coefficient r = -0.18; p-value = 0.03, with n = 155 exposed), but no significant correlation was observed between parent fipronil concentration and TSH (TSH Spearman's rank correlation coefficient r = -0.03; p-value = 0.86, with n = 33 exposed). With respect to Free T4 and TT4, no evidence of a significant correlation was reported between serum fipronil sulfone and these two thyroid hormone measures (Free T4 – r = - 0.08, p-value = 0.33; TT4 – r = 0.05, p-value = 0.55, with 155 exposed cases) or for serum fipronil and Free T4 or TT4 (Free T4 – r = -0.20, p-value = 0.27; TTF – r = -0.02, p-value = 0.90; with n = 33 exposed cases).

The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Study limitations included the cross-sectional study design and use of a single blood sample to quantify pesticide exposure and serum hormone levels. Since the pesticide exposure marker and the hormone levels were measured contemporaneously in this cross-sectional study, it is unclear if the associations observed provide direct evidence of a temporal relationship between pesticide exposure and the hormone levels assessed in the study, and this approach may not accurately reflect longitudinal or longer-term exposure patterns. The statistical analysis was minimally described and the bivariable analysis of the association between serum fipronil sulfone and thyroid hormone levels precluded the ability to adjust for potential confounding factors affecting the relationship between fipronil and thyroid function. Additionally, the analysis only considered those with occupational exposure to fipronil present at the time of the survey and did not consider the thyroid function in other factory workers without fipronil exposure which would have improved the interpretability and utility of the study.

EPA Conclusion

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between fipronil exposure and thyroid hormone effects. There were two available studies that examined thyroid hormone effects. Both studies were cross-sectional in design and assessed exposure by measuring fipronil sulfone concentrations in serum. One study (Kim et al., 2019) evaluated a large number of associations between the serum metabolite fipronil sulfone and several birth outcome parameters including thyroid hormone levels without correction for multiple comparisons or consideration that the measurements were correlated. The second study (Herin et al., 2011) reported findings from a bivariable analysis and did not consider potential confounding factors affecting the relationship between fipronil and thyroid effects. The findings are summarized in **Table 9** below.

Table 9: Summary of Epidemiological Evidence on Fipronil Exposure and Thyroid Effects.

Study	Study Population	Study Design[1]	Study Quality[2]	T3	T4	Free T3	Free T4	TSH
Kim et al. (2019)	Hospital-based birth-cohort of 51 parent-infant triads in South Korea (Neonates)	CS	L	↓●	⊘	↓●	⊘	⊘
Herin et al. (2011)	Workers in a pesticide manufacturing facility in France (Adults)	CS	L		⊘		⊘	↓●

⊘ No evidence of an association between exposure and outcome ($p > 0.05$).

● Evidence of a significant association ($p < 0.05$).

↑ - Positive association. ↓ - Negative association.

[39] We note that the authors state that exposure to fipronil in rats has been associated with ***increased*** serum TSH, not the decreased serum TSH observed here in this study.

[1] Study Design –*CS* = Cross-Sectional
[2] Study Quality –*L* = Low

3.6 Epidemiology Conclusion

OPP conducted a systematic review of the epidemiologic literature on fipronil exposure and identified two articles that investigated health outcomes including birth effects and thyroid hormone effects. OPP's conclusions on the available evidence for these outcomes are summarized below.

Birth Effects

- For birth effects including gestational age, birth weight, head circumference, birth length, ponderal index, and Apgar score at one minute, there is ***no evidence*** at this time to conclude that there is a clear associative or causal relationship between fipronil exposure and these birth effects as determined in a single study (Kim et al., 2019) that reported no evidence of an association between fipronil sulfone and the above mentioned birth effects among neonates in South Korea. Several limitations were noted for this study and this study was of low quality.
- For Apgar score at five minutes, there is ***insufficient evidence*** at this time to conclude that there is a clear associative or causal relationship with fipronil exposure. This determination was based on a single study (Kim et al., 2019) of cross-sectional design that reported evidence of a significant negative association between fipronil sulfone, a primary metabolite of fipronil, and Apgar score at five minutes. Again, several limitations were noted for this study and this study was of low quality.

Thyroid Effects

- Two studies investigated the relationship between fipronil and adverse effects on thyroid hormone concentrations in adults in France and neonates in South Korea. Both studies relied on cross-sectional study designs and were of low quality.
    - For thyroid hormones T4 and Free T4, there is ***no evidence*** at this time to conclude that there is a clear associative or causal relationship with fipronil exposure. This determination was based on two studies (Kim et al., 2019 and Herin et al., 2011) that both reported no evidence of a significant association between fipronil exposure and T4 and Free T4 levels. Several limitations were noted for both studies and both studies were of low quality.
    - For thyroid hormones T3 and Free T3, there is ***insufficient evidence*** at this time to conclude that there is a clear associative or causal relationship with fipronil exposure. This determination was based on a single study (Kim et al., 2019) that reported evidence of a significant negative association between fipronil sulfone, a primary metabolite of fipronil, and T3 and Free T3 levels measured in neonatal cord blood serum. Several limitations were noted for this study and this study was of low quality.
    - For thyroid hormone TSH, there is ***insufficient evidence*** at this time to conclude that there is a clear associative or causal relationship with fipronil exposure. This determination was based on two studies (Kim et al., 2019 and Herin et al., 2011) that reported mixed findings. Herin et al. (2011) reported a significant negative correlation between increasing fipronil sulfone levels in adults in France and decreasing TSH levels. Kim et al. (2019) reported a positive, but not statistically significant association between fipronil exposure and TSH levels in neonates in South Korea. Several limitations were noted for both studies and both studies were of low quality.

4 CONCLUSION

For this Fipronil Tier II Incident and Epidemiology Report, HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report. These health effects primarily most often involved the dermal, neurological, and ocular systems. HED did not identify any aberrant effects outside of those anticipated. These effects were generally mild/minor to moderate and resolved rapidly. In both IDS (78%) and SENSOR-Pesticides (65%) exposure to pet products were reported for most of the reported exposures. For NPIC (73%) and CA PISP (57%), post-application exposure following application to an individual's home was the most often reported exposure scenario. The IDS trend over time from 2009 to 2018 for fipronil incidents appears to be decreasing over time.

Epidemiological studies investigating the association between fipronil and health outcomes available in the open literature were reviewed. Overall, there was insufficient evidence to suggest a clear associative or causal relationship exists between fipronil exposure and the health outcomes investigated in the studies reported here. The Agency will continue to monitor the epidemiology data, and – if a concern is triggered – additional analysis will be conducted.

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6 APPENDIX A: DEATH, MAJOR AND MINOR SEVERITY INCIDENTS REPORTED TO MAIN IDS

Table 1. Death and Major Severity Fipronil Incidents Reported to Main IDS from 1/1/14 to 8/20/19

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Codes	Exposure Severity	Incident Description
027712 - 00002	4/26/2015	NY	065331-00004	FRONTLINE PLUS FOR CATS	129121, 105402	Major	A seven-year-old male was exposed to the product after it was applied to the family cats by his mother. He experienced facial swelling and was hospitalized. He was treated with antibiotics and the swelling improved.
027854 - 00001	6/17/2015		065331-00005	FRONTLINE PLUS FOR DOGS	105402, 129121	Major	An adult female applied the product to her dog. Approximately 1 to 1.5 hours later, her eyes started itching. Later that night, her eye was swollen shut, her face was hot/red and the right side of her face and part of the left side was swollen. She went to the Emergency Room and was given steroids and antihistamines.
031599 - 00001	11/3/2018	TALLAHASSEE, FL	002517-00134	FIP MT DOG SO 4-22LB	105402, 129121	Major	An adult male applied the product to his dog. That night, he experienced convulsions. The next morning, he felt nauseated.
031862 - 00002	12/1/2018	MADISON, WI	065331-00004	FRONTLINE PLUS CATS	105402, 129121	Major	An adult female applied the product to her cat. She experienced itching hives generalized around her body, and swelling of her feet and hands approximately six hours after the application.

Table 1. Death and Major Severity Fipronil Incidents Reported to Main IDS from 1/1/14 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
029630 - 00001	11/4/2016	EAST BROOKFIELD, MA	007969-00210	TERMIDOR SC INSECTICIDE	129121	Death, Moderate	A 47-year-old male passed away. He was exposed to the product annually was it was used to treat the outside of his home. The brother of the deceased was also exposed. After the initial treatment, they both experienced "a jittery feeling," shaking, muscle aches, joint pain, shortness of breath, hot flashes, sweating and heart palpitations. The caller reported that he moved out of his house and his symptoms improved.

Table 2. Moderate and Minor Severity Fipronil Incidents Reported to Main IDS from 1/1/17 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
029594 - 00003	1/10/2017	VA	002596-00178-065331	FRONTLINE GOLD FOR DOGS	129121, 105402, 129032	Minor	An adult female was applying the product to the dog and the tube cracked on the side and got all over her hand as well as getting on the dog. She wiped the excess on the dog and then she washed her hands off with hot water and soap. She does not know if the tingling sensation she is having on her hands if from the product or the hot water that she washed her hands with.

Table 2. Moderate and Minor Severity Fipronil Incidents Reported to Main IDS from 1/1/17 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
029744 - 00001	1/11/2017	PUEBLO, CO	053883-00312-002517	PET ARMOR PLUS IGR FOR DOGS IGR	129121, 124002	Moderate	The product which was meant for a large dog was applied to a small dog. Following the application an adult female experienced pallor, malaise and hot flashes. She was brought the hospital and her symptoms were diagnosed as a panic attack. She was given anti-anxiety medication and a sedative.
029652 - 00001	1/28/2017	PA	002596-00178-065331	FRONTLINE GOLD FOR DOGS	105402, 129121, 129032	Moderate	An adult male applied the products to his dog and cats a week ago as directed. Within 3 days his eyes were watering and itchy and he developed red skin on his arms and face and bump or hives on his arms and neck area. He did not wash his hands after applying the product. He has been to Urgent Care and was told to take oral Claritin and OTC drops for his eyes. His symptoms are not getting any better. His dog does sleep by his neck at night.
029773 - 00001	2/1/2017	ZOLFO SPRINGS, FL	007969-00210	TERMIDOR SC INSECTICIDE	129121	Moderate	A 68-year-old female was exposed when a pest control technician applied the product in the home while the family was present. Three to four days, she was experiencing a terrible skin rash. She saw her physician

Table 2. Moderate and Minor Severity Fipronil Incidents Reported to Main IDS from 1/1/17 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							a few days later and was given a topical cream which helped but did not resolved the issue. Two weeks later, she was in renal failure and was admitted to the hospital for emergency dialysis. She developed a skin infection. The treating physicians informed her that these symptoms are directly related her pre-existing medical conditions which were hypertension, diabetes and kidney failure. There is a total of nine people that live in the house including several children ranging in age from 2 to 16 years old. Symptoms reported by other members of the family include eye irritation, burning lips, upset stomach and headaches.
029677 - 00001	2/6/2017	MI	002596-00179-065331	FRONTLINE GOLD FOR CATS	129032, 129121, 105402	Moderate	An adult female opened the cap of the applicator and breathed in the odor of the liquid and her tongue began to swell up. She did not go to the ER or take any medications for the swelling. The cat had always been on the Frontline Plus.
029841 - 00001	2/17/2017	PA	065331-00005	FRONTLINE PLUS FOR DOGS	129121, 105402	Moderate	An adult female used the product on her dogs 6 weeks ago. Six weeks ago, she began feeling dizzy and

Table 2. Moderate and Minor Severity Fipronil Incidents Reported to Main IDS from 1/1/17 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							falling to the right. She has seen her neurologist: no diagnosis has been made. She is starting to feel better.
029876 - 00001	3/5/2017	NJ	070585-00013	PARASTAR PLUS FOR DOGS	129121, 129013	Moderate	A 10-year-old male developed hives after playing with his puppy. The product had been applied to the puppy prior to playing with the human patient. His mother noticed itchy hives on the boy around his neck and arms and all over his belly and back. The mother gave the human patient a dose of Benadryl and the human patient slept through the night. The next morning, the mother noticed hives on her son's leg, then he played with the puppy.
029829 - 00001	3/28/2017	KY	002596-00178-065331	FRONTLINE GOLD FOR DOGS	129121, 105402, 129032	Minor	An adult female was exposed to the product after it was applied to the dog. She was around the dog and petting the dog. The next day, she experienced nausea and dizziness.
030038 - 00003	3/31/2017	PA	065331-00005	FRONTLINE PLUS FOR DOGS	105402, 129121	Moderate	An adult female applied the product to her 6 dogs. Within two days after application she had vertigo and it felt like her head was disconnected. She went to the doctor and was given an antibiotic and medication for

Table 2. Moderate and Minor Severity Fipronil Incidents Reported to Main IDS from 1/1/17 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							the spinning. Today she realized one of her dog's sleeps by her head at night and the Frontline is the cause of her symptoms.
029836 - 00001	4/4/2017		002596-00178-065331	FRONTLINE GOLD FOR DOGS	105402, 129032, 129121	Minor	An adult female applied the product to her dog for the first time. The next morning, her hands were swollen, the washed her hands with soap and water. Her hands are now itchy and swollen.
029957 - 00011	4/13/2017	NH	002382-00187	EFFITIX TOPICAL SOLUTION FOR DOGS	129121, 109701	Moderate	An adult male applied the product to his dog. Over the next two weeks he developed dermatitis and sloughing on the palms of his hands.
030038 - 00004	4/15/2017	CT	065331-00005	FRONTLINE PLUS FOR DOGS	105402, 129121	Moderate	An adult female applied this product to her dogs and didn't have any physical contact with the product. The next day, however, she was holding the dogs on her lap in the car on the way to the dog park. She experienced blurred vision, dizziness, paleness and felt like her equilibrium was off.
030025 - 00002	4/22/2017	PHOENIX, AZ	007969-00210	TERMIDOR SC TERMITICIDE/ INSECTICIDE	129121	Moderate	A 23-year-old male was accidently sprayed in the face with the product at his job. He rinsed for about 2 minutes and went back to work. He went to bed feeling fine but when he woke up in the morning, he had blurry

Table 2. Moderate and Minor Severity Fipronil Incidents Reported to Main IDS from 1/1/17 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							vision. Two days later, his vision continued to be blurry. He reported that he was seen at a local emergency department where an unknown medication was administered to his eyes. Within 24 hours the blurred vision resolved and that no additional symptoms developed.
030131 - 00001	4/26/2017	NY	053883-00359-091300	SHIELDTEC FOR CATS	129121	Moderate	A 52-year-old male had the product applied to his cat. He used his finger to rub the product into the cat's skin but washed his hand afterwards. He also pet and kissed the cat. About four days later, he developed headache, profuse sweating, and an odor of ammonia to his sweat. The day after that, he developed nausea and vomiting and developed hives.
030150 - 00001	4/29/2017	GA	065331-00004	FRONTLINE PLUS FOR CATS	105402, 129121	Minor	An elderly female placed the product on the back of her cat's neck and got some residue on her forearm. At the time of exposure, her skin was a little irritated. Over the next two days, she developed pain in her leg and left knee. She applied a small amount of the drops to her knee to see if her knee

Table 2. Moderate and Minor Severity Fipronil Incidents Reported to Main IDS from 1/1/17 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							would be affected by the product.
030393 - 00001	5/1/2017	NJ	086230-00002-085495	PETARMOR FOR DOGS	129121	Moderate	Caller applied the product to his dog. The next day, his wife (a 57-year-old female) experienced issues breathing, blisters in her mouth, nausea, diarrhea, tingling lips and tongue, burning sensation in her chest. He brought her to the ER and she was placed on a steroid IV and a breathing treatment. She was sent home with an inhaler and diagnosed with an unknown allergy. After this occurred: he bathed the dog with a liquid dish soap and an oatmeal conditioner. 3-4 weeks later: the dog got wet in the rain and his wife reacted and she continues to react in this way when the dog gets wet.
030244 - 00001	5/26/2017	ALBUQUERQUE, NM	064240-00033	COMBAT QUICK KILL FOAM	129121	Moderate	A 60-year-old male was at the bus stop and a lady at the bus stop spray product into his face. He ingested and inhaled the product and the product contacted his eyes and nose. He experienced shortness of breath, blurry vision, lungs burn, bloody nose and mouth.

Table 2. Moderate and Minor Severity Fipronil Incidents Reported to Main IDS from 1/1/17 to 8/20/19							
Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
030194 - 00001	6/10/2017	OK	065331-00004	FRONTLINE PLUS FOR CATS	129121, 105402	Moderate	Caller states that she has applied this product to her cat Saturday night. Later that evening her 16-year-old son developed a rash on the arms. They went to the emergency room. The rash is now spreading all over his body.
030182 - 00001	6/16/2017	HADLEY, MI	002517-00134	PETARMOR PLUS FOR DOGS	105402, 129121	Moderate	Caller applied the product to her dog and believes she got the product on her arm in the process, although she does not remember getting the product on her. Not long after application, she her left forearm began to itch. Later m the day, it turned red and blistered. She then washed the area with soap and water and applied antibiotic ointment to the area.
030399 - 00001	6/22/2017	PA	002596-00178-065331	FRONTLINE GOLD FOR DOGS	129032, 129121, 105402	Moderate	An adult female used the product on her dog 3 months ago. She cuddles with the dog a lot. For the last 3 months she has had nerve pain in her left arm. She has been going to physical therapy for the arm but it is not getting any better.
030412 - 00001	7/2/2017	BALTIMORE, MD	088052-00013-089609	PETACTION PLUS FOR DOGS	129121, 105402	Moderate	An adult female applied the product to her dogs. At that time, site had been bitten by ants. She developed a rash with blisters and weeping. She saw her doctor and used

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							cortisone cream which helped. She was diagnosed with contact dermatitis. Ten days later, she went back and was prescribed oral prednisone. The rash is healing, and her skin is peeling. When she hugged her dog, the rash became aggravated.
030147 - 00001	7/5/2017	TX	002596-00178-065331	FRONTLINE GOLD FOR DOGS	129121, 105402, 129032	Minor	An adult female caller applied the product to her dogs and then touched the application area. She may have touched her mouth; her lips feel funny.
030147 - 00002	7/5/2017	NY	002596-00178-065331	FRONTLINE GOLD FOR DOGS	129121, 129032, 105402	Minor	An adult female got some of the product on her hands. One area of her hand feels irritated.
030414 - 00001	7/17/2017		065331-00004	FRONTLINE PLUS CATS	129121, 105402	Moderate	An adult female put the product on her cats and developed allergic skin.
030326 - 00001	7/21/2017	TN	065331-00004	FRONTLINE PLUS CATS	105402, 129121	Moderate	Caller says that she applied the product to the cats two days before she allowed her 3-year-old daughter to touch the cat. After her daughter touched the cat, she broke out in hives all over her body they have been back and forth to the emergency room with her for the last two days. She also had some vomiting during this time.

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							Her daughter is allergic to many things.
030214 - 00001	7/24/2017		002596-00179-065331	FRONTLINE GOLD FOR CATS	105402, 129032, 129121	Minor	An adult male applied the product a couple of days ago and since then, has had diarrhea and hasn't been feeling well.
030326 - 00002	7/31/2017	CA	065331-00004	FRONTLINE PLUS CATS	129121, 105402	Moderate	An adult female applied the product to the cat. Ever since she applied the product she has been sick and she knows that she the product is the cause of the symptoms. She experienced kidneys hurting badly, sharp kidney pain, nausea, and brain fog.
030483 - 00001	8/12/2017	NC	065331-00005	FRONTLINE PLUS FOR DOGS	129121, 105402	Moderate	An adult male applied the product to his dogs and developed hives and itchiness.
030414 - 00002	8/21/2017		065331-00001	FRONTLINE SPRAY	129121	Moderate	An adult female applied the product to her pet. She got some on her hand and rubbed her forehead. She experienced skin irritation and welts since.
030356 - 00001	8/29/2017	OK	002596-00179-065331	FRONTLINE GOLD FOR CATS	105402, 129032, 129121	Minor	An adult female put the product on her pets and gave the cat an insulin shot and thinks she got the product on her hand. The next morning, she experienced red splotches/dots all over her

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							body like an allergic reaction.
030483 - 00002	9/6/2017	PA	065331-00004	FRONTLINE PLUS FOR CATS	129121, 105402	Moderate	An adult female used the products on her four pets. She experienced ocular irritation, dizziness, nausea, shaking and vertigo. The symptoms subside when she leaves the house but return when she goes back into the house.
030476 - 00002	9/7/2017	CO	002382-00187	EFFIPROTIX TOPICAL SOLUTION FOR DOGS	129121, 109701	Moderate	An adult female applied the product and got it on her fingers. Two days later, she experienced tingling in her hands and feet, and burning eyes and trouble focusing. Her husband woke up 3 days post application with hives.
030405 - 00001	9/12/2017	FL	002596-00178-065331	FRONTLINE GOLD FOR DOGS	105402, 129121, 129032	Minor	An adult female touched the application site on the dog and then touched her eye 10 to 15 minutes ago. Her eye is irritated.
030374 - 00001	9/13/2017	IL	002596-00178-065331	FRONTLINE GOLD FOR DOGS	129032, 105402, 129121	Minor	An adult female had trouble with the package and caused it to ooze out of the side on under her fingernails. It burned a bit and she washed, and the symptoms subsided.
030557 - 00002	9/28/2017	FL	065331-00004	FRONTLINE PLUS CATS	105402, 129121	Moderate	An adult female applied the product to her cat and her eyes started itching that night. Over the next two days, the area around her eyes was red. By the third

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							day post exposure, her entire face was swollen. She went to the ER and received a steroid. When she was done with the steroid, her symptoms returned.
030557 - 00001	9/30/2017	MI	065331-00004	FRONTLINE PLUS CATS	105402, 129121	Moderate	A 71-year-old male may have pet his cat while the product was still drying. The next day, he had a rash on his arms.
030538 - 00004	10/3/2017	NIAGRA FALLS, NY	007969-00210	TERMIDOR SC TERMITICIDE/ INSECTICIDE	129121	Moderate	The product was applied by a pest control company to control yellow jackets inside the house. The product was applied all over the house, including walls, carpets, clothing, and bedding. The adult male homeowner develops asthma symptoms following exposure to the product.
030523 - 00001	10/7/2017	TX	002596-00179-065331	FRONTLINE GOLD FOR CATS	129032, 129121, 105402	Minor	An adult female applied the product to her cat. She experiences tingling after petting the cat or touching the cats bedding.
030599 - 00002	11/1/2017	CAMP HILL, PA	002517-00135	PETARMOR PLUS FLEA & TICK SQUEEZE-ON	129121, 105402	Moderate	A 14-year-old female had an allergic reaction (hives) to the product when she held the family cat that had previously been treated by her mother with the product.
030577 - 00001	11/20/2017	NJ	002596-00179-065331	FRONTLINE GOLD FOR CATS	105402, 129032, 129121	Minor	An adult female got some of the product on her hands and then washed her hands. She experienced itching.

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
030649 - 00001	11/20/2017	TAMPA, FL	007969-00329	TERMIDOR HE	129121	Moderate	An adult male was sick with flu-like symptoms. He started feeling better and used the product to clean lawn furniture. Three days later, he started feeling sick again.
030681 - 00001	12/2/2017	FORT MILL, SC	002596-00179-065331	FRONTLINE GOLD FOR CATS	129032, 105402, 129121	Minor	A 74-year-old female applied the product to her cats every month. Sometime after the third application of the product to her cats, she developed a rash on her arms.
030681 - 00002	12/4/2017	WEXFORD, PA	002596-00179-065331	FRONTLINE GOLD FOR CATS	105402, 129121, 129032	Minor	A 50-year-old female applied the product on her cats. Within five days, she started to nice a rash on her right legs that spread to her armpits. The dermatologist diagnosed her with an allergic reaction.
030669 - 00001	12/28/2017	HOMER, AK	002596-00178-065331	FRONTLINE GOLD FOR DOGS	105402, 129121, 129032	Minor	A 57-year-old woman applied the product to her dog. Then she touched her lips and her lips became numb.
030681 - 00003	1/2/2018	MI	002596-00179-065331	FRONTLINE GOLD FOR CATS	129121, 105402, 129032	Minor	An adult female accidentally was exposed to the product when it leaked in its case and she got some on her hands. She experienced dermal pain and irritation.
030791 - 00001	1/2/2018	STATELINE, NV	065331-00001	FRONTLINE SPRAY	129121	Moderate	A 39-year-old male used the product and accidentally got some in his eyes and inhaled it while he was spraying his

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							dog. He experienced slightly red and irritated eyes and agitation and lightheadedness.
030815 - 00001	1/5/2018	KY	007969-00210	TERMIDOR SC TERMITICIDE/ INSECTICIDE	129121	Moderate	An adult female used the product. Two months later, she experienced check, neck and shoulder pain, twitching and muscle pain, and shortness of breath.
030753 - 00001	2/5/2018	CLIFTON, NJ	002596-00179-065331	FRONTLINE GOLD FOR CATS	105402, 129032, 129121	Minor	An adult female applied the product to her cats. She experienced erythema and pruritus on her hands.
030867 - 00002	2/18/2018	MATTAPOISETT, MA	002596-00178-065331	FRONTLINE GOLD DOG	129032, 129121, 105402	Minor	A 10-year-old female was exposed after her mother applied the product to the family dog. Within 24 hours of the product application, she developed a pruritic rash on her arm.
030867 - 00001	3/1/2018	WAUKESHA, WI	002596-00178-065331	FRONTLINE GOLD DOG	105402, 129032, 129121	Minor	A 25-year-old male got the product into his eyes when he opened the product to put it on his dog. He experienced redness and slight irritation.
031177 - 00002	5/6/2018	PORT CHESTER, NY	002517-00134-088832	FLEA 5X PLUS FOR DOGS	105402, 129121	Moderate	Caller states she applied 1 dose of product topically to her dog. She forgot to tell her son that she had applied the product and not to touch the dog. Her son had been hugging and laying on the dog. The next morning, her son started experiencing vertigo issues. He was taken to ER and the doctor was

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							unable to determine a cause for the symptoms. MRI and CAT scans were done, but no reason for the vertigo has been found yet. Her son has been put on an antibiotic because a tick has bitten him on his scalp 2 days before this event. Sinus inflammation was found but it was not an infection. No diagnosis was given, nothing found wrong with her son. The vertigo resolved on its own.
031520 - 00003	6/20/2018	COLONIAL BEACH, VA	002517-00145-065331	FRONTLINE TRITAK FOR CATS	105402, 128965, 129121	Moderate	A 52-year-old female cannot confirm, but suspects that her husband may have been poisoning her over the last two to three months by pouring an unknown volume of FRONTLINE TRITAK FOR CATS (1014PI2) into her drinks because during said time frame. she's experienced chronic jitteriness and nose bleeds which she's unsuccessfully treated with saline nasal flushes.
031424 - 00001	7/4/2018	SAN ANTONIO, TX	007969-00210	TERMIDOR SC INSECTICIDE	129121	Moderate	The Caller applied this product around the perimeter of his house two years prior to the call in 2016. Two to three months prior to the call, caller started to auger and dig up parts of his yard

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							where this product was possibly applied. Sometime later, he, his daughter, and his dog all started to develop itching all over after being in the back yard. His daughter had also developed rashes that come and go that seems to pop up after she has been in the back yard. She went to the dermatologist. At the time of the dermatology appointment, she was not having an outbreak. From what caller described to the doctor, the doctor thought it sounded like eczema. He prescribed her a prescription cream which has helped. But he, his dog, and his daughter continue to itch when they come in from the backyard.
031460 - 00002	7/20/2018	SIOUX CITY, IA	002596-00178-065331	FRONTLINE GOLD DOG	105402, 129032, 129121	Moderate	A 49-year-old female applied the product to her dog. She did not wash her hand following the application. Approximately 45 minutes later, she ate and licked her fingers after which she became dizzy, light-headed and her tongue felt funny. Approximately two weeks later, she experienced loose stools and headaches.

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
031459 - 00001	7/30/2018	SOUTH AMBOY, NJ	088052-00013-089609	PETLOCK PLUS FOR DOGS	105402, 129121	Moderate	An adult female applied the products to her dogs. She did not wear gloves, but did wash her hands. Following the application, she experienced an itchy rash with hives on her arms.
031460 - 00001	8/5/2018	TX	065331-00005	FRONTLINE PLUS DOG	129121, 105402	Moderate	A 44-year-old male was exposed to the product after it had been applied to his dog by the breeder. He played with the treated puppy and his lips began to swell. The next day, his lips continued to swell and he developed urticaria on his arms, sides, and back and his palms are pruritic. He went to Urgent Care and was treated with steroids.
031460 - 00003	8/18/2018	JACKSONVILLE, FL	065331-00002	FRONTLINE TOP SPOT CATS	129121	Moderate	A 65-year-old male was exposed when his daughter mistakenly dispensed an entire vile of the product into the patient's breathing machine. He was on oxygen therapy following open heart surgery that had been performed a week prior. He experienced coughing, a slight sensation of his throat closing, chapped lips and tongue.
031520 - 00001	9/5/2018	WATERLOO, SC	065331-00004	FRONTLINE PLUS CATS	129121, 105402	Moderate	A 70-year-old female applied FRONTLNE PLUS FOR CATS (lot unknown) to her cat. That evening, she

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							kissed the cat and that night, the cat slept with her. She awoke with swollen lips. She used Biotin mouth wash which helped decrease the edema. The patient also reported that her breathing is slightly affected, but the way its affected is unknown. On approximately the same date, the patient's daughter-in-law sprayed Lysol in the house where the cat had access to.
031520 - 00002	9/13/2018	RICKMAN, IN	065331-00005	FRONTLINE PLUS DOGS 89-132 LBS	129121, 105402	Moderate	A 74-year-old female attempted to give 1 vial of FRONTLINE PLUS OOG 89-132 LBS (M63950AR) SC to her pet. In doing so. she accidentally pricked her hand injecting an unknown amount of medication under her skin. An unknown amount of time later, she washed her hands with soap for 2 minutes. The patient's hand became swollen and she had trouble breathing. At the time of call, patient was not dyspneic during the call at any point and when questioned further she said she's very anxious about the incident. The patient is a Type II diabetic and has rheumatoid arthritis (RA). She is also allergic to unknown medication.

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031520 - 00004	9/22/2018	SAN DIEGO, CA	065331-00005	FRONTLINE PLUS DOG 5-22 LBS	129121, 105402	Moderate	A 65-year-old female was exposed to FRONTLINE PLUS DOG 5-22 LBS after she adopted a dog that was treated at the Humane Society. Two days after application, she experienced onset of chronic periorbital edema, a severe migraine, and nausea. The reporter has a history of multiple chemical sensitivities, fragrance sensitivities, and migraines.
031520 - 00005	9/26/2018	WILLIAMSPORT, PA	065331-00005	FRONTLINE PLUS DOG 23-44 LBS	105402, 129121	Moderate	A 58-year-old female applied FRONTLINE PLUS DOG 23-44 LBS (R60107AX) to her dog. She pet the dog either at or around the application site. She subsequently got an unknown volume of product on her hands, but didn't wash them for several hours. On several occasions while walking her dog, the patient experienced dizziness requiring her to sit down and rest. After drinking some water. the symptom resolved. The reporter has an unknown genetic cardiac-valvular condition which often causes her to become dizzy, requiring that she rest to recover.

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
031704 - 00001	10/9/2018	SUISUN, CA	007969-00210	TERMIDOR SC TERMITICIDE/ INSECTICIDE	129121	Minor	An adult female was exposed to three products when they were applied to her home. She left during the application and when she returned she began to experience symptoms including eye irritation, cold skin, breast pain, hoarse voice, shortness of breath, trouble balancing, confusion, coughing yellow phlegm, fast heart rate, and elevated blood pressure. She went to the emergency department; no medications or treatments were given and no diagnosis was made.
031797 - 00001	10/18/2018	GRAND BLANK, MI	002596-00178-065331	FRONTLINE GOLD DOGS 5-22 LBS	129032, 129121, 105402	Moderate	An adult female was exposed to the product. She developed itchy hives on her face and arms.
031713 - 00001	11/16/2018	ALGONQUIN, IL	065331-00005	FRONTLINE PLUS DOGS 5-22 LBS	129121, 105402	Moderate	A 39-year-old female accidentally got the product in her eye when she opened it. Within 30 minutes of exposure, she experienced burning and stinging. She went to her optometrist and had to have a layer of the sclera removed and was prescribed antibiotic eye drops.
032044 - 00002	12/13/2018	ROLLING HILLS, CA	065331-00005	FRONTLINE PLUS FOR DOGS	105402, 129121	Minor	An adult male used the product and got it on his skin.

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
031862 - 00001	12/21/2018	HAYWARD, CA	065331-00004	FRONTLINE PLUS CATS	105402, 129121	Moderate	A 54-year-old female applied the products to her cat and dog. The next day, she developed a bumpy, red rash on her back, chest, arms, and legs. Her dermatologist believed the reaction was to something the pet owner ate and not the pet products.
032137 - 00001	1/15/2019	OTTINE, TX	065331-00004	FRONTLINE PLUS CATS	105402, 129121	Moderate	An 85-year-old female was exposed to a cat that had been treated with the product by a family member. After the first treatment, the patient developed a rash inside her right elbow where the cat lies. A rash was also noted on the patient's neck, chest, and leg area. After the second treatment (one month later), she developed clear blisters on her neck. The patient had been applying cortisone cream to some areas. It was noted that the patient has a history of seasonal allergies. asthma, diabetes, and oral cancer. She is on a liquid diet and has not been introduced to new foods.
031975 - 00001	2/7/2019	BROKEN ARROW, OK	065331-00005	FRONTLINE PLUS FOR DOGS 5-22 LBS	129121, 105402	Moderate	A 21-year-old female accidentally splashed the product in her eye when she was opening the product.

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							She rinsed her eye. She experienced blurred vision.
032056 - 00002	3/4/2019	ARROYO GRANDE, CA	065331-00005	FRONTLINE PLUS DOG 5-22 LBS	105402, 129121	Moderate	A 63-year-old male applied FRONTLINE PLUS DOG 5-22 LBS (560810X) to his dogs. A tiny drop landed on his is forearm, and was washed off instantly. Later that day, he began to have trouble inhaling fully, and if he moves his upper torso, his ribs ache and he had runny stool once. On follow-up he does not believe that the signs that he had were associated with the potential exposure to the product. His wife came home later that same day with similar concerns and she had no exposure to the product.
032056 - 00001	3/5/2019	GRANITE BAY, CA	065331-00005	FRONTLINE PLUS DOG 5-22 LBS	105402, 129121	Moderate	A 67-year-old female applied the product to her dogs. Shortly after application, her face, lip and tongue began to swell. She went to an urgent care and was diagnosed with angioedema. She fully recovered 24 to 30 hours. She applied the product to her dog two more times over the next two months. Both time she experienced the same symptoms of face, lip and tongue swelling.

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
032137 - 00003	4/7/2019	NAZARETH, PA	065331-00007	CERTIFECT FOR DOGS 45-88 LBS	129121, 106201, 105402	Moderate	A 50-year-old female applied a dose of CERTIFECT FOR DOGS 45-88 LBS to her dog. Later that day, the owner developed some pimples on her face. The next day, she developed a blotchy red, bumpy, burning rash on her face and cheeks. Her face became swollen and the rash spread down toward her neck. Her skin also feels dry and she has some mild itching.
032149 - 00003	4/7/2019	TAMPA, FL	064248-00011	MAXFORCE ROACH BAIT STATIONS	129121	Moderate	A 15-month-old child touched the product and placed it in her mouth. She developed a fever. She was treated with ibuprofen and acetaminophen and returned to normal after 5 days.
032150 - 00001	4/13/2019	LAGUNA BEACH, CA	007969-00210	TERMIDOR SC TERMITICIDE/ INSECTICIDE	129121	Moderate	An adult female was exposed to the product when it was used in home. The pest control company plugged 8 holes in the sheet rock in her bedroom. She slept in the bedroom that night. The next day, she experienced “flu like symptoms" including vomiting, dizziness, sneezing, coughing, sore throat, headache and fatigue. She went to urgent care and the doctor was reported to

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							have stated that he was unable to determine what was causing her symptoms and gave her a Z pack (antibiotic).
032213 - 00001	5/19/2019	SAINT LOUIS, MO	065331-00005	FRONTLINE PLUS DOGS 23-44 LBS	105402, 129121	Moderate	A 7-year-old female accidentally touched her dog (that had been treated by her dad) on the spot where the product had been applied and then touched her eye. She experienced stinging and burning in her eye.
032361 - 00001	5/25/2019	FL	065331-00005	FRONTLINE PLUS DOGS 23-44 LBS	129121, 105402	Moderate	An adult female got the product on her fingers when she was applying it to her dog. Within 24 hours her finger became swollen and painful. She also experienced lethargy. She has a history of Lupus and breast cancer.
032361 - 00002	6/4/2019	MINERAL, VA	065331-00005	FRONTLINE PLUS DOGS 23-44 LBS	129121, 105402	Moderate	A 75-year-old male got the product on his hand when he applied it to his dog. Within 20 minutes of exposure, he experienced burning. He washed his hands with soap and water. He experienced burning again, when he pet his dog. Three days later, his elbow and wrist became sore.
032361 - 00003	6/21/2019	BELLINGHAM, WA	065331-00001	FRONTLINE SPRAY	129121	Moderate	A 23-year-old pregnant female believes she was exposed following treatment near air vents, outside the

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Incident Package Report	**Incident Date**	**Location**	**Reg Number**	**Product Name**	**PC Codes**	**Exposure Severity**	**Incident Description**
							motel she was staying in. She turned on the vents in the evening and the next morning experienced sneezing, erythema, lethargy, abdominal pain, dysuria, and polyuria. She went to MD who said her symptoms were not related to the product.

7 APPENDIX B: SUMMARY OF EPIDEMIOLOGIC STUDIES AND STUDY QUALITY ASSESSMENT

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Fipronil Results	Study Quality
Herin et al. (2011	2008	Factory workers in France study	Cross-sectional n = 159 (~10% of all workers in the factory)	Serum fipronil or fipronil sulfone concentration Survey	Serum concentration of thyroid hormones TSH, Free T4, TT4	Evidence of an association between serum fipronil sulfone and serum TSH (correlation coefficient = -0.18; p-value = 0.03, n = 155 fipronil exposed cases). No evidence of an association with fipronil sulfone and other thyroid hormones Free T4 and TT4, p-values > 0.05 n = 155 fipronil exposed cases).	Low
Kim et al. (2019)	2013-2015	South Korea Hospital Patients	Cross-sectional n = 59 parent-infant triad	Serum fipronil and fipronil sulfone	Serum concentration of T3, Free T3, Free T4, T4, TSH Birth effects documented in medical records	Evidence of an association between serum fipronil sulfone and serum T3 (β = -0.105, 95% CI: -0.19, -0.02) and FreeT3 (β = -0.021, 95% CI: -0.040, -0.002). No evidence of a significant association between T4 (β = -0.677, 95% CI: -1.79, -0.435), Free T4 (β = -0.033, 95% CI: -0.163, 0.096) and TSH (β = -0.537, 95% CI: -6.745, 7.818).	Low